A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP6520.

Finding the Right Fit: Highly Selective Binding by the Thyroid Hormone Receptor

Charles W. Schmidt

https://doi.org/10.1289/EHP6520

Chemicals that alter how thyroid hormones work in the body have the potential to cause serious health problems. Thyroid hormones regulate metabolism and development, and disruption of their normal functioning raises concerns, especially for neurodevelopmental outcomes in children.[1,2] Evidence shows that several industrial pollutants interfere with thyroid hormone signaling.[3,4,5,6] Those discoveries have fueled speculation that many other chemicals might interact with thyroid hormone receptors (TRs) to cause similar effects. However, a study published in *Environmental Health Perspectives* suggests TR binding with environmental chemicals is more selective than previously suspected.[7]

To investigate, scientists used *in vitro* methods to screen the 8,305 chemicals in the Tox21 chemical library. The results showed that just 11 of the screened chemicals interacted with TRs directly. "The findings imply that direct effects on TR from chemicals occur rarely," says senior author Keith Houck, a research toxicologist in the U.S. Environmental Protection Agency's Center for Computational Toxicology and Exposure. According to Houck, other components of the hypothalamic–pituitary–thyroid axis—the system responsible for controlling the balance of thyroid hormones—should take priority over TRs for additional screening efforts.

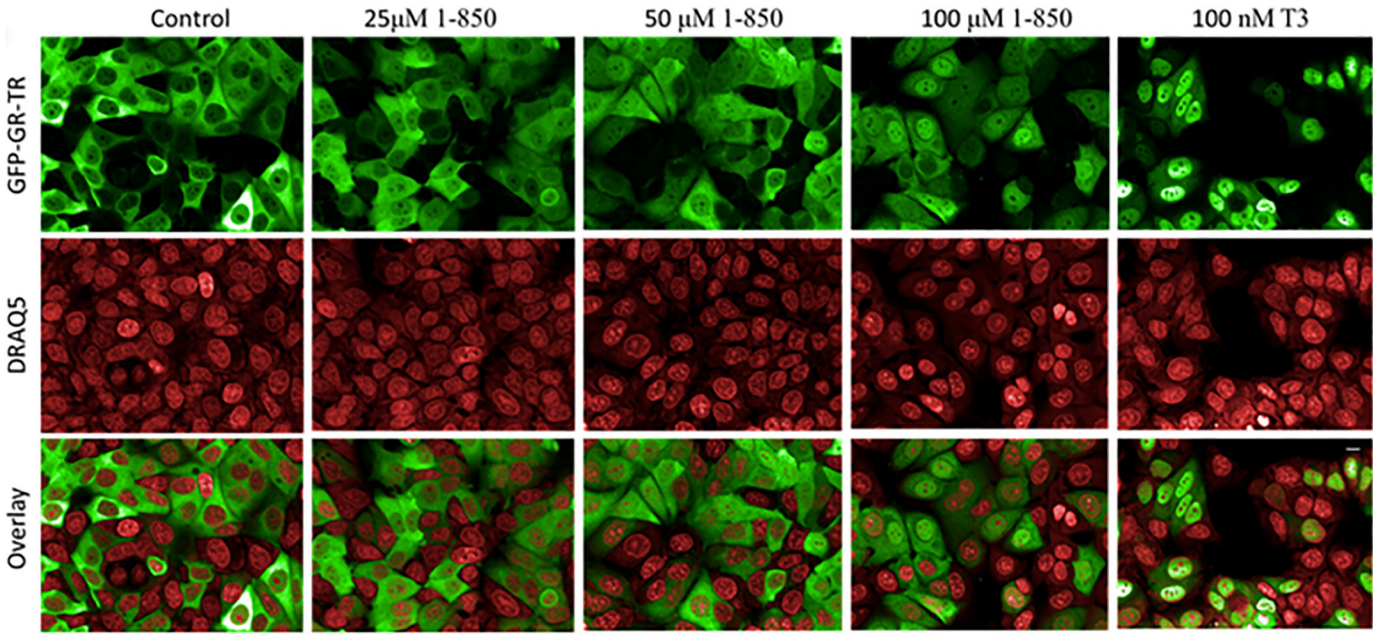
TRs are a group of nuclear receptors. They interact with other receptors, along with thyroid hormones, to bind to DNA, thereby regulating the expression of specific genes.

As a preliminary step in the new study, all Tox21 chemicals were screened using the GH3-TRE-Luc cell line. This cell line includes a reporter gene that is regulated by TR–hormone signaling.[4] The reporter gene produces a bioluminescent protein that glows more brightly when activated, in this case by exposures to chemicals. A dimmer glow indicates decreased TR activity.

Active compounds—those that increased or decreased luminescence of cells, relative to unexposed cells—then underwent additional assays for further characterization. One of these assays tests chemicals for interaction with a molecule called the retinoid-X receptor (RXR), which forms a DNA-binding complex with TRs. Unlike chemicals that act directly on TRs, the RXR-binding compounds can activate TRs indirectly. Yet, because scientists know less about the indirect effects from chemicals acting on RXR, "we're less confident about extrapolating from current studies to potential hazards," Houck says.

Additional assays were used to investigate more specifically how chemicals might be interacting with TRs. Among the 11 compounds identified in the study as directly binding with TRs, 8 were agonists and 3 were antagonists.

Seth Kullman, a professor of toxicology at North Carolina State University who was not involved in the research, says the findings bolster emerging evidence that TRs are very selective in the types of ligands they interact with. Other nuclear receptors in the endocrine system, such as the androgen and estrogen receptors, are more promiscuous by comparison, Kullman says, meaning they bind a wider variety of chemical compounds. But given their important roles in a variety of endocrine processes, TRs and their indirect interactions remain an important priority for toxicology research, he adds.



This figure illustrates the model that Houck and colleagues developed to test for TR activity. Top row: The investigators tagged an engineered TR with a protein that glows green, showing its subcellular location when introduced into a human breast cancer cell line. Here the receptor is shown in the presence of a TR antagonist (indicated by "1-850") or agonist (indicated by "T3"). Middle row: To measure the amount of TR in the cell nucleus, the investigators labeled the nuclei with a fluorescent red dye. Bottom row: The combination of tagged TR and stained nuclei enabled the team to demonstrate the degree to which a chemical would cause TR to transfer from the cell cytoplasm to the nucleus—in other words, how much the chemical might interfere with TR signaling. Image: Paul-Friedman et al. (2019); DOI: 10.1289/EHP5314.

David Volz, an associate professor at the University of California, Riverside, who also was not involved in the study, says it was important that the researchers used a battery of tests for chemical screening, especially given that *in vitro* assays do not fully represent responses in living animals. "If you don't use complementary assays, you risk walking away with erroneous conclusions," he says. "That's why it is significant that the authors used a weight-of-the-evidence approach. It will be interesting to see where this research goes from here."

Charles W. Schmidt, MS, an award-winning science writer from Portland, ME, writes for *Scientific American*, *Science*, *Undark*, various *Nature* publications, and many other magazines, research journals, and websites.

References

1. Ghassabian A, Trasande L. 2018. Disruption in thyroid signaling pathway: a mechanism for the effect of endocrine-disrupting chemicals on child development. Front Endocrinol (Lausanne) 9:204, PMID: 29760680, https://doi.org/10.3389/fendo.2018.00204.
2. Mughal BB, Fini JB, Demeneix BA. 2018. Thyroid-disrupting chemicals and brain development: an update. Endocr Connect 7(4):R160–R186, PMID: 29572405, https://doi.org/10.1530/EC-18-0029.
3. Calsolaro V, Pasqualetti G, Niccolai F, Caraccio N, Monzani F. 2017. Thyroid disrupting chemicals. Int J Mol Sci 18(12):2583, PMID: 29194390, https://doi.org/10.3390/ijms18122583.
4. Freitas J, Cano P, Craig-Veit C, Goodson ML, Furlow JD, Murk AJ. 2011. Detection of thyroid hormone receptor disruptors by a novel stable *in vitro* reporter gene assay. Toxicol In Vitro 25(1):257–266, PMID: 20732405, https://doi.org/10.1016/j.tiv.2010.08.013.
5. Kollitz EM, De Carbonnel L, Stapleton HM, Ferguson PL. 2018. The affinity of brominated phenolic compounds for human and zebrafish thyroid receptor β: influence of chemical structure. Toxicol Sci 163(1):226–239, PMID: 29409039, https://doi.org/10.1093/toxsci/kfy028.
6. Kollitz EM, Kassotis CD, Hoffman K, Ferguson PL, Sosa JA, Stapleton HM. 2018. Chemical mixtures isolated from house dust disrupt thyroid receptor β signaling. Environ Sci Technol 52(20):11857–11864, PMID: 30212187, https://doi.org/10.1021/acs.est.8b03283.
7. Paul-Friedman K, Martin M, Crofton KM, Hsu C-W, Sakamuru S, Zhao J, et al. 2019. Limited chemical structural diversity found to modulate thyroid hormone receptor in the Tox21 chemical library. Environ Health Perspect 127(9):97009, PMID: 31566444, https://doi.org/10.1289/EHP5314.